HEPATITIS C

Before 1990, patients who received blood transfusions were vulnerable to an unknown infectious agent of liver disease then known only as non-A, non-B hepatitis. However, after being cloned and genetically sequenced more than a decade ago, the hepatitis C virus (HCV) was identified as the cause of most of these unidentified, transfusion-related liver infections.

Hepatitis C continues to emerge as a serious infectious disease in the United States and worldwide. Chronic hepatitis C infection can lead to liver inflammation, cirrhosis, and cancer. HCV infects more than 170 million people worldwide, including 3.9 million people in the United States.[35] About 25,000 new U.S. infections occur each year,[36] and liver failure resulting from HCV infection is the leading cause of liver transplants in the United States.

Fortunately, rapid improvements in HCV diagnostics, including tests that can detect both antibodies to the virus and the virus itself, have made the supply of blood and blood products in this country safe from HCV contamination. Today, injection drug users are at highest risk of infection. Sexual transmission also occurs, especially among people with multiple partners; other transmission routes are also possible, including exposure to contaminated blood. Approximately 55 to 85 percent of infected people become chronic carriers of the virus.[37] However, because people with chronic HCV infection often show no overt symptoms even as their livers are being attacked by the virus, many current carriers do not know they are infected.

NIAID has aggressively expanded its HCV research program through its Framework for Progress on Hepatitis C. In collaboration with participating Institutes and Centers, NIAID developed an NIH-wide framework that incorporates the different missions of NIH into a cohesive global plan for hepatitis C research. The final plan was reviewed by outside experts and has been approved by NIH Institute and Center Directors and the NIH Director. The plan identified the following research goals:

- Understand transmission modes to develop effective intervention strategies.
- Understand pathogenic mechanisms and disease progression to develop new treatment.
- Characterize host immune responses to infection in order to develop new vaccines and therapies.
- Define viral replication and recovery during therapy.
- Investigate clinical manifestations in order to develop methods to noninvasively evaluate disease state, predict outcomes, and prevent or reverse disease progression.
- Define effective prevention and intervention strategies to improve health.

The tools needed to achieve these goals include tissue culture systems, small-animal models, well-defined clinical cohorts, and research and reference reagents and tools.

Current hepatitis C therapies include various forms of interferon, an interferon-ribavirin combination, and long-lasting forms of interferon with and without ribavirin. Each new therapy has resulted in improved response rates. However, these drugs have a significantly lower success rate in African Americans and in patients infected with the viral strain—called genotype 1—that predominates in the United States; a total of six distinct genotypes have been identified. Studies suggest that African Americans infected with genotype 1 and treated with interferon for HCV have a lower end-of-treatment response than do Whites. NIAID funds both basic research on HCV and product development for viral therapeutic targets, including inhibitors of viral components such as the polymerase, protease,

helicase, and internal ribosome entry site, as well as other viral components critical for replication.

Extramural investigators developed HCV cell lines that are now validated as *in vitro* antiviral screening tools. NIAID supports two of these systems via its *in vitro* screening contract programs; they can be accessed through this program by both academic and corporate scientists. Further information is available at *www.niaid.nih.gov/dmid/viral*.

A major reason that many people cannot clear HCV infection is that the virus subverts the immune response through a process called immune evasion. Thus, defining and overriding these evasion strategies through rational design of vaccines and immunotherapies is an important area of emphasis for NIAID-supported HCV research and development.

NIAID intramural and extramural investigators also are conducting many research activities that will help pave the way for the development of HCV vaccines. Recent efforts to develop HCV vaccines have been related primarily to the identification of immune responses—both protective and evasive—in infected humans and experimentally-infected chimpanzees. NIAID recently launched a phase I trial of Chiron Corporation's prototype E1E2 HCV vaccine, intended to evaluate the safety, tolerability, and immunogenicity of this vaccine candidate in healthy, uninfected human subjects.

The extramural program of NIAID has initiated two activities to further enhance its research and development activities. The first activity is the acquisition and provision of HCV research reagents, which are now provided through the AIDS Research and Reference Reagent Program (*www.aidsreagent.org*). Other HCV-related reagents are available through the NIH Tetramer Facility (*www.niaid.nih.gov/reposit/tetramer/index.html*) and the NIAID Reference Reagent Repository (*www.bratonbiotech.com/braton11.htm*). The second activity is the development of an annotated HCV sequence database by Los Alamos National Laboratories (*http://hcv.lanl.gov/content/hcv-db/index*).

In 2002, NIAID cosponsored the "Management of Hepatitis C: 2002" Consensus Development Conference. The meeting was convened to provide an update to a 1997 conference on the same topic. Among the recommendations for future research in its report,[38] the panel gave top priority to the development of reliable and reproducible HCV cultures, which will advance the understanding of HCV biology and mechanisms of drug resistance and aid vaccine development. The panel also urged the establishment of a hepatitis research network that would conduct research into the natural history, prevention, and treatment of hepatitis C.

NIAID supports a robust hepatitis C research portfolio that encompasses many of these areas. In particular, NIAID supports the Hepatitis C Cooperative Research Centers Network, which unites basic and clinical researchers investigating hepatitis C infection and disease to identify new and better means of prevention and treatment. Through this network, NIAID supports clinical research that emphasizes studies in special populations heavily affected by HCV such as African Americans, who tend to respond poorly to standard therapies. NIAID also continues to help support the ancillary studies of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial of the National Institute of Diabetes and Digestive and Kidney Diseases. This trial is evaluating the impact of long-term therapy on disease progression, including virologic and immunologic responses and their association with recovery.

Scientists in NIAID's Division of Intramural Research are conducting research to answer key questions about HCV pathogenesis and the host immune response in order to develop an effective HCV vaccine and better hepatitis C treatments. Along the way, they are improving the tools used in hepatitis research. They are also developing

critical research reagents and sharing them with researchers around the country.

For example, NIAID scientists collaborated with colleagues in France to demonstrate that a new *in vitro* test to detect and quantify virus neutralizing antibodies worked as well as a more cumbersome test that requires the use of chimpanzees.[39] This finding will help researchers identify the specific portions of HCV that induce protective antibodies and promote the development of an effective hepatitis C vaccine.

The scientists then used the new assay to test batches of commercial immune globulin manufactured before and after the initiation of HCV screening of the donated blood plasma used to make it. They found that batches manufactured before HCV screening contained high levels of neutralizing antibody and were not associated with HCV infections in recipients. In contrast, immune globulins manufactured after initiation of screening for HCV lacked neutralizing antibodies and were associated with many cases of hepatitis C in recipients. This work conclusively demonstrates that neutralizing antibodies protect humans from HCV infection and provides for the first time a rational basis for passive antibody-based prevention of hepatitis C.

Basic research, as well as vaccine and therapeutic development, would be greatly aided by the development of a small-animal model in which to study HCV and to fine-tune candidate vaccine formulations. To this end, NIAID researchers are working to determine whether the GB virus B (GBV-B), a monkey virus that is the closest relative of HCV, is a suitable surrogate for HCV in experimental studies. If so, then the tamarin monkey could be used for *in vivo* studies and greatly reduce the need for chimpanzees for HCV research. Work is this area has been encouraging. For example, NIAID scientists recently reported that the p7 protein of HCV is critical for infectivity and represents a new target for HCV drug development.[40] They have since gone on to show that a p7-like protein of GBV-B exists and is also essential for infectivity, strengthening the relevance of GBV-B as a model of HCV.